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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
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01/17/2002

Bernhard Hauer

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03/18/2010

NOVAK DRUCE DELUCA + QUIGG LLP

1300 EYE STREET NW

SUITE 1000 WEST TOWER

WASHINGTON, DC 20005

EXAMINER

PAK, YONG D

ART UNIT

PAPER NUMBER

1652

MAIL DATE

DELIVERY MODE

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PAPER

Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Office Action Summary	Application No. 10/031,241	Applicant(s) HAUER ET AL.	
	Examiner YONG D. PAK	Art Unit 1652	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

- 1) ☒ Responsive to communication(s) filed on 09 December 2009.
- 2a) ☒ This action is **FINAL**. 2b) ☐ This action is non-final.
- 3) ☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

- 4) ☒ Claim(s) 11,12,14-18 and 23-30 is/are pending in the application.
- 4a) Of the above claim(s) _____ is/are withdrawn from consideration.
- 5) ☐ Claim(s) _____ is/are allowed.
- 6) ☒ Claim(s) 11-12, 14-18, and 23-30 is/are rejected.
- 7) ☐ Claim(s) _____ is/are objected to.
- 8) ☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

- 9) ☐ The specification is objected to by the Examiner.
- 10) ☐ The drawing(s) filed on _____ is/are: a) ☐ accepted or b) ☐ objected to by the Examiner.
Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).
Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).
- 11) ☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

- 12) ☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).
- a) ☐ All b) ☐ Some * c) ☐ None of:
- ☐ Certified copies of the priority documents have been received.
 - ☐ Certified copies of the priority documents have been received in Application No. _____.
 - ☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

- | | |
|---|---|
| 1) <input type="checkbox"/> Notice of References Cited (PTO-892) | 4) <input type="checkbox"/> Interview Summary (PTO-413) |
| 2) <input type="checkbox"/> Notice of Draftperson's Patent Drawing Review (PTO-948) | Paper No(s)/Mail Date. _____ |
| 3) <input type="checkbox"/> Information Disclosure Statement(s) (PTO/SB/08) | 5) <input type="checkbox"/> Notice of Informal Patent Application |
| Paper No(s)/Mail Date _____ | 6) <input type="checkbox"/> Other: _____ |

DETAILED ACTION

This application is a 371 of PCT/EP00/07251.

The amendment filed on December 9, 2009, amending claims 11-12, 14-15, and 26-29, has been entered.

Claims 11-12, 14-18, and 23-30 and are under consideration.

Response to Arguments

Applicant's amendment and arguments filed on December 20, 2007, have been fully considered and are deemed to be persuasive to overcome the objection previously applied.

Claim Objections

In view of the amendment of claim 35, the objection to claim 35 has been **withdrawn**.

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

(a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negated by the manner in which the invention was made.

Claims 11-12, 14, 16-18, and 23-30 remain rejected under 35 U.S.C. 103(a) as being unpatentable over Estabrook et al. in view of Creaser et al., Fish et al., Reipa et al. and Oliver et al.

Claim 11-12, 14, 16-18, and 23-30 drawn to a method for the enzymatic production of terminally or subterminally hydroxylated fatty acids comprising hydroxylating fatty acids in the presence of an electron donor system, a cytochrome P450 monooxygenase or a mutant of a cytochrome P450 of SEQ ID NO:35 having a mutation at position 87, and oxygen, wherein said electron donor system is zinc dust/Co(III)sepulchrate.

Estabrook et al. (*Methods in Enzymology* – form PTO-1449) discloses a method for the enzymatic production of terminally or subterminally hydroxylated fatty acids comprising hydroxylating fatty acids in the presence of an electron donor system, a cytochrome P450 monooxygenase, oxygen, chloride ions and a hydrogen peroxide-cleaving enzyme, wherein said fatty acid is a C-12 fatty acid and wherein said electron donor system comprises a Co(III)sepulchrate mediator of Creaser et al.. Estabrook, et al. teaches that said mediator “retains chirality during reversible oxidation-reduction” (page 45, 1st paragraph).

The difference between the reference of Estabrook et al. and the instant invention is that the reference of Estabrook et al. does not teach a method of producing terminally or subterminally hydroxylated fatty acids using a Zn metal in powder form as

the source of non-electrode bound electrons or a mutant of a cytochrome P450 of SEQ ID NO:35 having a mutation at position 87.

Creaser et al. (J. Am. Chem. Soc – form 1449) discloses a Zn/Co(III)sepulchrate electron donor system, which pioneered for the use of Co(III)sepulchrate as mediators in electrochemical reactions (Faulkner et al. – form PTO-1449, Reipa et al. – US Patent 6,126,795 and Roberts et al. – US Patent 6,492,132), wherein the Co(III)sepulchrate mediator is the same mediator used by Estabrook et al. Creaser et al. teaches that Zn dust, a source of non-electrode bound electrons, causes reduction of the Co(III)sepulchrate mediator within seconds (page 3181).

Fish et al. (Talanta. 1997 May;44(5):939-45 - form PTO-892) discloses that interference of organic matter with electrode response is a been well known problem in the art (page 939) and offers methods to lessen said interference. Reipa et al. (US Patent No. 6,126,795 - form PTO-892) discloses disadvantages of a system using electrodes and P450 enzymes in hydroxylating organic compounds: irreversible adsorption of protein constituents leading to electrode fouling and protein denaturation (Column 2, lines 34-55).

Oliver et al. (Biochemistry 1997, 36, 1567-1572 – form PTO-892) discloses a mutant of SEQ ID NO:35 having a F87A mutation which hydroxylates fatty acids at the ω position, unlike the wildtype enzyme (abstract and page 1567).

Therefore, in combining the teachings of Estabrook et al., Creaser et al., Fish et al., Reipa et al. and Oliver et al., it would have been obvious to one having ordinary skill

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in the art to modify the method of Estabrook et al. in hydroxylating fatty acids at the ω by using the mutant cytochrome P450 monooxygenase of Oliver et al. and using Zn dust as the non-electrode source of electrons as taught by Creaser et al. One of ordinary skill in the art would have been motivated to use the mutant cytochrome P450 monooxygenase of Oliver et al. because said mutant is able to catalyze ω hydroxylation of fatty acids. One of ordinary skill in the art would have been motivated to use Zn dust as a source of non-electrode bound electrons because Creaser et al. teaches that Zn dust causes immediate reduction, Zn dust is widely available (Sigma), Reipa et al. teaches disadvantages of a system using electrodes and P450 enzymes in hydroxylating organic compounds (irreversible adsorption of protein constituents leading to electrode fouling and protein denaturation) thus decreasing its efficacy, and Fish et al. teaches that electrode fouling due to organic matter is a problem well known in the art. One of ordinary skill in the art would have had a reasonable expectation of success since Estabrook et al. teaches a method of hydroxylating fatty acids with cytochrome P450 monooxygenases by replacing NADPH with an electrochemically generated reduction by the mediator Co(III)sepulchrate, Creaser et al. teaches a method of generating two electrons using the mediator Co(III)sepulchrate and Zn dust as the source of electrons, and Oliver et al. teaches a mutant that catalyzes ω hydroxylation of fatty acids.

Therefore, the above references render claims 11-12, 14, 16-18, and 23-30 *prima facie* obvious to one of ordinary skill in the art.

In response to the previous Office Action, applicants have traversed the above rejection.

Applicants argue that Fish et al. and Reipa et al. do not provide a motivation to replace the electrode system employed by Estabrook et al. by a non-electrode bound source of electrons such as metal powder or Zn power because (1) Fish et al. disclose that fouling of Cd electrodes may be prevented by covering the electrode with a dialysis membrane and Estabrook et al. uses a membrane covered oxygen electrode and (2) Reipa et al. indirectly acknowledge that problems arising from using electrodes in enzyme catalysis mentioned by Reipa et al. (Column 2, lines 34-55) are not encountered in the process of Estabrook et al. since Reipa et al. only mentions the use of the cobalt mediator as the drawback. Examiner respectfully disagrees.

(1) Covering electrodes is one solution to a well known problem associated with using electrodes in enzyme catalysis. Said solution does not necessarily prevent one of ordinary skill to explore other solutions available in the art nor criticize, discredit, or otherwise discourage the solution claimed. Since an electron donor system comprising a non-electrode source of electrons (Zn dust and Co(III)sepulchrates mediator), such as that disclosed by Creaser et al., was known and available in the art and Zn dust causes immediate reduction and Zn dust is widely available, one having ordinary skill in the art would have been motivated to use Zn dust as a source of non-electrode bound electrons.

(2) Reipa et al.'s silence regarding problems associated with using electrodes of an electron donor system comprising an electrode and a Co(III)sepulchrates mediator

does not imply that the only drawback of the electron donor system used by Estabrook et al. is the cobalt mediator.

Applicants also argue that Creaser et al. does not provide any guidance, teaching or suggestion to employ a combination of zinc dust and Co(III) sepulchrate in a biochemical system/reaction. Examiner respectfully disagrees. In response to applicant's arguments against the references individually, one cannot show nonobviousness by attacking references individually where the rejections are based on combinations of references. See *In re Keller*, 642 F.2d 413, 208 USPQ 871 (CCPA 1981); *In re Merck & Co.*, 800 F.2d 1091, 231 USPQ 375 (Fed. Cir. 1986). The instant rejection is based on the combined teachings of Estabrook et al., Creaser et al., Fish et al., Reipa et al. and Oliver et al.. The Co(III)sepulchrate mediator of Creaser et al. is the same mediator used by Estabrook et al. Creaser et al. also teaches that Zn dust, a source of non-electrode bound electrons, causes reduction of the Co(III)sepulchrate mediator within seconds (page 3181). One of ordinary skill in the art would have been motivated to use Zn dust as a source of non-electrode bound electrons because Creaser et al. teaches that Zn dust causes immediate reduction, Zn dust is widely available (Sigma), Reipa et al. teaches disadvantages of a system using electrodes and P450 enzymes in hydroxylating organic compounds (irreversible adsorption of protein constituents leading to electrode fouling and protein denaturation) thus decreasing its efficacy, and Fish et al. teaches that electrode fouling due to organic matter is a problem well known in the art.

Applicants also argue that a person of ordinary skill in the art clearly had no reasonable expectation that a combination of zinc dust and Co(III) sepulchrates could be successfully employed in the process of Estabrook et al. instead of the membrane-covered electrode since the combination of Zn dust and Co(III) sepulchrates reaction has a relative reaction almost twice as high as that of the electron donor system of Estabrook et al. Examiner respectfully disagrees. Creaser et al. teaches a method of generating two electrons using the mediator Co(III)sepulchrates and Zn dust as the source of electrons. Since Creaser et al. teaches that Zn dust causes immediate reduction, Examiner takes the position that the “superior results” asserted by applicants is not unexpected. Obviousness does not require absolute predictability, but only a reasonable expectation of success. Applicants are advised to prove evidence showing there was no reasonable expectation of success in using zinc dust and Co(III) sepulchrates in the method of Estabrook et al.

Double Patenting

The nonstatutory double patenting rejection is based on a judicially created doctrine grounded in public policy (a policy reflected in the statute) so as to prevent the unjustified or improper timewise extension of the “right to exclude” granted by a patent and to prevent possible harassment by multiple assignees. A nonstatutory obviousness-type double patenting rejection is appropriate where the conflicting claims are not identical, but at least one examined application claim is not patentably distinct from the reference claim(s) because the examined application claim is either anticipated by, or would have been obvious over, the reference claim(s). See, e.g., *In re Berg*, 140 F.3d 1428, 46 USPQ2d 1226 (Fed. Cir. 1998); *In re Goodman*, 11 F.3d 1046, 29 USPQ2d 2010 (Fed. Cir. 1993); *In re Longi*, 759 F.2d 887, 225 USPQ 645 (Fed. Cir. 1985); *In re Van Ornum*, 686 F.2d 937, 214 USPQ 761 (CCPA 1982); *In re Vogel*, 422 F.2d 438, 164 USPQ 619 (CCPA 1970); and *In re Thorington*, 418 F.2d 528, 163 USPQ 644 (CCPA 1969).

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A timely filed terminal disclaimer in compliance with 37 CFR 1.321(c) or 1.321(d) may be used to overcome an actual or provisional rejection based on a nonstatutory double patenting ground provided the conflicting application or patent either is shown to be commonly owned with this application, or claims an invention made as a result of activities undertaken within the scope of a joint research agreement.

Effective January 1, 1994, a registered attorney or agent of record may sign a terminal disclaimer. A terminal disclaimer signed by the assignee must fully comply with 37 CFR 3.73(b).

Claims 11-12, 14-18, and 23-30 are rejected on the ground of nonstatutory obviousness-type double patenting as being unpatentable over claims 1-5 of U.S.

Patent No. 7,531,335 in view of Estabrook et al., Creaser, Fish et al., and Reipa et al.

U.S. Patent No. 7,531,335 discloses a process for the enzymatic production of terminally or subterminally hydroxylated fatty acids comprising hydroxylating fatty acids in the presence of variant of the P450 monooxygenase of SEQ ID NO:2, wherein the variant has a F87A or F87V, L188K, A74G, R47F, and V26T. SEQ ID NO:2 and SEQ ID NO:35 of the instant application are 100% identical.

The difference between the reference of U.S. Patent No. 7,531,335 and the instant invention is that U.S. Patent No. 7,531,335 does not teach a method of producing terminally or subterminally hydroxylated fatty acids using a Zn metal in powder form as the source of non-electrode bound electrons.

Estabrook et al. (*Methods in Enzymology* – form PTO-1449) discloses a method for the enzymatic production of terminally or subterminally hydroxylated fatty acids comprising hydroxylating fatty acids in the presence of an electron donor system instead of using NADPH or NADH, a cytochrome P450 monooxygenase, oxygen, chloride ions and a hydrogen peroxide-cleaving enzyme, wherein said fatty acid is a C-12 fatty acid and wherein said electron donor system comprises a Co(III)sepulchrate

mediator of Creaser et al.. Estabrook, et al. teaches that said mediator “retains chirality during reversible oxidation-reduction” (page 45, 1st paragraph).

Creaser et al. (J. Am. Chem. Soc – form 1449) discloses a Zn/Co(III)sepulchrate electron donor system, which pioneered for the use of Co(III)sepulchrate as mediators in electrochemical reactions (Faulkner et al. – form PTO-1449, Reipa et al. – US Patent 6,126,795 and Roberts et al. – US Patent 6,492,132), wherein the Co(III)sepulchrate mediator is the same mediator used by Estabrook et al. Creaser et al. teaches that Zn dust, a source of non-electrode bound electrons, causes reduction of the Co(III)sepulchrate mediator within seconds (page 3181).

Fish et al. (Talanta. 1997 May;44(5):939-45 - form PTO-892) discloses that interference of organic matter with electrode response is a been well known problem in the art (page 939) and offers methods to lessen said interference. Reipa et al. (US Patent No. 6,126,795 - form PTO-892) discloses disadvantages of a system using electrodes and P450 enzymes in hydroxylating organic compounds: irreversible adsorption of protein constituents leading to electrode fouling and protein denaturation (Column 2, lines 34-55).

Therefore, in combining the teachings of Estabrook et al., Creaser et al., Fish et al., and Reipa et al. it would have been obvious to one having ordinary skill in the art to modify the method of US Patent 7,531,335 by hydroxylating fatty acids at the ω by using the electron donor system taught by Estabrook and using Zn dust as the non-electrode source of elections as taught by Creaser et al. One of ordinary skill in the art would have been motivated to use the above described electron donor system instead

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of using NADPH or NADH. One of ordinary skill in the art would have been motivated to use Zn dust as a source of non-electrode bound electrons because Creaser et al. teaches that Zn dust causes immediate reduction, Zn dust is widely available (Sigma), Reipa et al. teaches disadvantages of a system using electrodes and P450 enzymes in hydroxylating organic compounds (irreversible adsorption of protein constituents leading to electrode fouling and protein denaturation) thus decreasing its efficacy, and Fish et al. teaches that electrode fouling due to organic matter is a problem well known in the art. One of ordinary skill in the art would have had a reasonable expectation of success since Estabrook et al. teaches a method of hydroxylating fatty acids with cytochrome P450 monooxygenases by replacing NADPH with an electrochemically generated reduction by the mediator Co(III)sepulchrate, Creaser et al. teaches a method of generating two electrons using the mediator Co(III)sepulchrate and Zn dust as the source of electrons, and Oliver et al. teaches a mutant that catalyzes ω hydroxylation of fatty acids.

In response to the previous Office Action, applicants have traversed the above rejection.

Applicants argue that Fish et al. and Reipa et al. do not provide a motivation to replace the electrode system of Estabrook et al., as discussed above. See above for rebuttal of said arguments.

Conclusion

None of the claims are allowable.

THIS ACTION IS MADE FINAL. Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire **THREE MONTHS** from the mailing date of this action. In the event a first reply is filed within **TWO MONTHS** of the mailing date of this final action and the advisory action is not mailed until after the end of the **THREE-MONTH** shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than **SIX MONTHS** from the mailing date of this final action.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Yong Pak whose telephone number is 571-272-0935. The examiner can normally be reached 6:30 A.M. to 5:00 P.M. Monday through Thursday.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Andrew Wang can be reached on 571-272-0811. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to the receptionist whose telephone number is 571-272-1600.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see <http://pair-direct.uspto.gov>. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll free).

/Yong D Pak/
Primary Examiner, Art Unit 1652